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EXAMINER

GOLDBERG, JEANINE ANNE

ART UNIT PAPER NUMBER

1634

DATE MAILED: 02/26/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/705,587

Applicant(s)

Y.YU ET AL.

Examiner

Jeanine A Goldberg

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 06 December 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 13-22 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 13-22 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

### **DETAILED ACTION**

1. This action is in response to the papers filed December 6, 2002. Currently, claims 13-22 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.
2. Any objections and rejections not reiterated below are hereby withdrawn in view of applicant's arguments and the amendments made to the claims.
3. This action contains new grounds of rejection necessitated by amendment.

### ***New Matter***

4. Claims 13-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the amended claims, reference to "concentrations between about 50 picomolar and 1400 picomolar" are included. The amendment proposes that the new claim language is supported in the specification at pages 25-34. The specification teaches the sensitivity and specificity of the assay of the instant invention is described with data showing detection of antisense oligonucleotides at levels as low as about 50 picomolar and as high as 2000 picomolar. However, the specification does not describe or discuss "concentrations between about 50 picomolar and 1400 picomolar". Instead the specification describes four specific examples of concentration, namely 50, 100, 500 and 1500 pM. The specification does not appear to contemplate a range. Furthermore,

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the specification does not contemplate a concentration of 1400 pM. It is presumed that applicant has added the limitation of 1400 pM to overcome the prior art of record.

As provided by the MPEP, "New or amended claims which introduce elements or limitations which are not supported by the as-filed disclosure violate the written description requirement. See, e.g., *In re Lukach*, 442 F.2d 967, 169 USPQ 795 (CCPA 1971) (subgenus range was not supported by generic disclosure and specific example within the subgenus range); *In re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972) (a subgenus is not necessarily described by a genus encompassing it and a species upon which it reads).

This description does not support "concentrations between about 50 picomolar and 1400 picomolar". The concept of ""concentrations between about 50 picomolar and 1400 picomolar"" does not appear to be part of the originally filed invention. Therefore, "concentrations between about 50 picomolar and 1400 picomolar"" constitutes new matter. Applicant is required to cancel the new matter in the reply to this Office Action.

***New Grounds of Rejection Necessitated by Amendment***

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 13, 15, 20-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Temsami (Analytical Biochemistry, Vol. 215, page 54-58, 1993) in view of Boutet et al. (Biochemical and Biophysical Res. Comm., Vol. 268, pages 92-98, February 2000) in further view of Impraim et al (US Pat. 6,228,578, May 2001).

Temsami et al (herein referred to as Temsami) teaches a method for the quantification of oligonucleotide phosphorothioates in biological fluids and tissues. Temsami teaches a method which uses membrane-bound oligodeoxynucleotide phosphorothioate and then hybridized with labeled complementary oligonucleotides and exposed to X-ray film. Temsami teaches that the sensitivity of detection allows monitoring of pharmacokinetics of oligonucleotides in bodily fluids. Temsami teaches using digoxigen as a chemiluminescent method for detecting a label (limitations of Claim 20)(page 56). Temsami teaches detecting oligo nucleotide 1 and 2 at

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concentrations as low as 1.5 ng (Figure 2, page 55, col. 2). Oligonucleotide 1 and 2 are 24 and 20 nucleotides in length, respectively.

Temsami does not specifically teach detecting between 50 and 1400 picomolar by forming hybrids prior to contacting with a solid support, nor teaches using a nuclease to degrade non-hybridized probes.

However, Boutet et al. (herein referred to as Boutet) teaches a method of real-time monitoring of the hybridization reaction by quantifying oligonucleotides in biological samples. Boutet teaches sensitivities for phosphodiester and phosphorothioate oligonucleotides as 0.2 and 0.8 pmol/ml in plasma. Oligo A was used for analysis. Oligonucleotide A and ATS are 15 nucleotides in length (average MW of 4200pg/picomole). The assay was performed in a final volume of 250 microliters (page 93, col. 2). Therefore, the sensitivity of detection was 1.05 ng. The method of Boutet teaches a <sup>real</sup> ~~rat~~-time monitoring of hybridization which involves oligonucleotides labeled with biotin and Str-APC acceptor, allophycocyanin, covalently linked to streptavidin.

Moreover, Impraim et al (herein referred to as Impraim) teaches a method for detecting an oligonucleotide in a bodily fluid by (a) preparing a bodily fluid (b) contacting the liquid with a probe complementary to said oligonucleotide, wherein the probe comprises a detectable marker and a binding moiety (c) placing the fluid in contact with a solid support to which a binding partner of said binding moiety is attached (d) removing any oligonucleotide from said sample that has not formed a hybrid moiety (e) contacting said fluid with a single strand specific nuclease to degrade the non-hybridized oligonucleotides (f) removing any unbound detectable marker from said liquid

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sample and (g) detecting a label associated with the marker. Impraim specifically detecting a non-radioactive hybridization assay for detecting of genetic defects, microbial infections or viral infections (abstract). The sample, such as blood, is incubated with nucleic acid probes specific for target nucleic acids (limitations of Claim 13a, b)(abstract, col. 5, line 1). It is noted that nicking of the nucleic acids is not only optional, but would also constitute preparation of a fluid for analytical detection to form a liquid sample. The hybrids are captured onto a solid phase, such as a test tube or polystyrene bead, coated with an anti-hybrid antibody (limitations of Claim 1c)(abstract, col. 5, lines 9-12). Impraim teaches that after capture, any excess sample is removed from the capture tube (limitations of Claim 13d)(col. 9, lines 20-21). The unhybridized probe is eliminated with an enzyme, such as RNAase, that degrades non-hybridized probe (limitations of Claim 13e)(abstract, col. 4, lines 42-45). Impraim teaches that "the purpose of the RNA digestion enzyme is to degrade non-hybridized probe that may be bound to the tube. It is important to remove the excess probe because secondary structures in the nucleic acid can be recognized by the detection means, resulting in elevated assay background" (col. 9, lines 25-30). Impraim teaches a wash step following the digestion (col. 9, lines 50-55). And finally the bound hybrid is detected using labels such as an enzyme, fluorescent molecule or a biotin-avidin conjugate (limitations of Claim 13g, 9) (abstract, col. 5, lines 37-39). Impraim also teaches that the captured hybrid can be detected with a direct labeled RNA probe, such as an enzyme conjugated hybridization probe or a hapten-modified probe that is subsequently detected by a labeled anti-hapten antibody. Impraim teaches that the method provides

a cost-effective, sensitive, non-radioactive hybridization assay for the detection and quantification of nucleic acids in a sample (col. 4). Further the hybridization assay provides an assay in which sample preparation is simple and rapid, does not involve extractions, precipitation, centrifugation, or other purification methods (col. 4).

Additionally, the method provides a non-radioactive hybridization assay having minimal false positives, allows accurate quantitative monitoring test for the level of microbial or viral infections (col. 4).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Temsmani with the sensitive method of Boutet and the method of Impraim. The ordinary artisan would have recognized the explicit benefits of cost-effective, sensitive and non-radioactive hybridization assay of the method of Impraim and would have been motivated to have monitored the pharmacokinetics of oligonucleotides with phosphorothioates. There would have been a reasonable expectation of success that a method of forming hybrids prior to the attachment to the solid support would work given the teachings of Impraim. Impraim, Boutet, and Temsamani each teach that their methods are useful for monitoring of nucleic acids. Thus, the ordinary artisan would therefore have recognized that the probe may be either attached to the solid support prior to the hybridization with the oligonucleotide or a hybrid may be formed followed by attachment to a solid support. Further, the ordinary artisan would have been motivated to have removed unhybridized probes with a nuclease for the expected benefit of removing the probes from the solution and to eliminate any interference.



### **Response to Arguments**

The response traverses the rejection.

The response asserts that "neither reference, alone or when combined, would teach or suggest detection of antisense oligonucleotides at concentrations between 50 and 1400 picomolar. This argument has been thoroughly reviewed, but is not found persuasive because while the combination of Tamsamani and Imprim do not specifically teach that detection could not be performed, Tamsamani teaches detection as low as 1.5 ng. However, the art, as exemplified by Boutet teaches the detection of oligonucleotides in quantities as low as 1.05 ng. Therefore, at the time the invention was made, there was a reasonable expectation of success of detection of antisense oligonucleotides at low levels.

Thus for the reasons above and those already of record, the rejection is maintained.

7. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tamsami (Analytical Biochemistry, Vol. 215, page 54-58, 1993) in view of Imprim et al (US Pat. 6,228,578, May 2001) as applied to Claims 1, 15, 21 above, and further in view of de Serres et al (Analytical Biochemistry, Vol. 233, pages 228-233, 1996).

While Imprim teaches sampling from blood and Tamsami teaches sampling serum. Neither Tamsami nor Imprim specifically teaches sampling from plasma.

However, de Serres teaches a method of determining plasma concentrations of a compound 4003W94, a 15 base phosphorothioate antisense deoxyribonucleotides that is

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currently under preclinical evaluation for the treatment of restenosis following coronary artery angioplasty.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Temsami in view of Impraim to sample plasma. The ordinary artisan would be motivated to sampled plasma for monitoring the concentration of antisense molecules.

### **Response to Arguments**

The response traverses the rejection. The response asserts that adding Serres which teaches detection of oligonucleotides in plasma in a "very different method" can not render the invention obvious. This argument has been reviewed but is not convincing because the response has not pointed out any technical reasons why detection of nucleic acids using the method of Temsamani in view of Impraim in plasma as taught by Serres is not obvious. The ordinary artisan would have been motivated to have used the method of Temsamani in view of Impraim which has numerous explicit benefits for detection of oligonucleotides in plasma as taught by Serres. Thus for the reasons above and those already of record, the rejection is maintained.

8. Claims 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Temsami (Analytical Biochemistry, Vol. 215, page 54-58, 1993) in view of Boutet et al. (Biochemical and Biophysical Res. Comm., Vol. 268, pages 92-98, February 2000) in further view of Impraim et al (US Pat. 6,228,578, May 2001) as applied to Claims 13,

15, 20-21 above and further in view of Lind et al (Nucleic Acids Research Vol. 26, No. 16, pages 3694-3699, 1998).

Temsami, Boutet, nor Impraim does not specifically teach incorporating a 2'-O-methoxyethyl- modified nucleotide into the oligonucleotide.

However, Lind teaches that the 2' sugar-substituted o'(2-methoxyethyl) (MOE) has increased nuclease resistance and a very high binding affinity. The MOE-substituted oligonucleotides have shown outstanding promise as antisense agents in several disease states and are presently being investigated in clinical trials for treatment of CMV retinitis. Lind further teaches that "one of the biggest advantages of the MOE substitution is the improvement in binding affinity, which is greater than many similar 2' modifications".(page 2694, col. 2).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Temsami, Boutet and Impraim for detecting nucleic acids with a modification at the 2' position of at least one sugar moiety. The ordinary artisan would have readily realized that the modification at the 2' position would allow for improved binding affinity and nuclease resistance, which is ideal in hybridization assays such as the assay taught by Impraim.

### **Response to Arguments**

The response traverses the rejection. The response asserts in the response filed December 6, 2002, that the primary reference of Impraim does not teach the invention, therefore, the combination of a secondary reference does not render the invention obvious. This argument has been reviewed but is not convincing because the rejection

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of the primary reference is maintained for the reasons indicated above. Thus for the reasons above and those already of record, the rejection is maintained.

9. Claims 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Temsami (Analytical Biochemistry, Vol. 215, page 54-58, 1993) in view of Boutet et al. (Biochemical and Biophysical Res. Comm., Vol. 268, pages 92-98, February 2000) in further view of Impraim et al (US Pat. 6,228,578, May 2001) as applied to Claims 13, 15, 20-21 above and further in view of Prosnyak et al (Genomics, Vol. 21, page 490-494, 1994).

Neither Temsami, Boutet, nor Impraim specifically teaches using a modified base such as 5-methylcytosine.

However, Prosnyak et al (herein referred to as Prosnyak) teaches that 5-methylcytosine is a modification that increases duplex stability. An oligonucleotide which contains 5-methylcytosine is shown to bind DNA more specifically than the corresponding unmodified oligonucleotide.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the detection method of Temsami, Boutet and Impraim to include a modified base such as 5-methylcytosine for the expected benefit taught by Prosnyak. The ordinary artisan would be motivated to substitute a 5-methylcytosine in order to create a more stable duplex for detection purposes.

#### **Response to Arguments**

The response traverses the rejection. The response asserts in the response filed December 6, 2002, that the primary reference of Impraim does not teach the invention, therefore, the combination of a secondary reference does not render the invention obvious. This argument has been reviewed but is not convincing because the rejection of the primary reference is maintained for the reasons indicated above. Thus for the reasons above and those already of record, the rejection is maintained.

10. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Temsami (Analytical Biochemistry, Vol. 215, page 54-58, 1993) in view of Boutet et al. (Biochemical and Biophysical Res. Comm., Vol. 268, pages 92-98, February 2000) in further view of Impraim et al (US Pat. 6,228,578, May 2001) as applied to Claims 13, 15, 20-21 above and further in view of Lundin (Nucleic Acids Research, Vol. 25, No. 12, page 2535-2536, 1997).

Temsami, Boutet, nor Impraim specifically teaches using S1 nuclease as the single-stranded specific nuclease.

However, Lundin teaches use of S1 nuclease to degrade single-stranded DNA.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Temsami, Boutet and Impraim to use S1 nuclease to degrade single-stranded DNA. The ordinary artisan would be motivated to have substituted a single-stranded DNA nuclease for RNAase when the probes used are DNA. Since, the ordinary artisan would be motivated to

degrade any non-hybridized probes, any nuclease which accomplishes this purpose would be an obvious substitute since they are functional equivalents.

### **Response to Arguments**

The response traverses the rejection. The response asserts in the response filed December 6, 2002, that the primary reference of Impraim does not teach the invention, therefore, the combination of a secondary reference does not render the invention obvious. This argument has been reviewed but is not convincing because the rejection of the primary reference is maintained for the reasons indicated above.

Thus for the reasons above and those already of record, the rejection is maintained.

### ***Conclusion***

**11. No claims allowable over the art.**

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any


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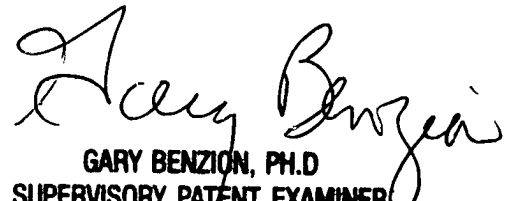
extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

  
Jeanine Goldberg  
February 12, 2003

  
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